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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/507,466 | 09/10/2004 | Marc Ostermeier | 56908(71699) | 1259 |
| 21874 7590 06/19/2007 EDWARDS ANGELL PALMER & DODGE LLP P.O. BOX 55874 BOSTON, MA 02205 | | | EXAMINER CHEN, SHIN LIN | |
| | | | ART UNIT 1632 | PAPER NUMBER |
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/507,466

Applicant(s)

OSTERMEIER, MARC

Examiner

Shin-Lin Chen

Art Unit

1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 29 March 2007.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-8, 14, 26, 30, 32, 38, 39, 41 and 45-47 is/are pending in the application.
- 4a) Of the above claim(s) 26, 30, 32, 38, 39 and 41 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-8, 14 and 45-47 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

Art Unit: 1632

DETAILED ACTION

Applicant's amendment filed 3-29-07 has been entered. Claims 1, 7 and 14 have been amended. Claims 45-47 have been added. Claims 1-8, 14, 26, 30, 32, 38, 39, 41 and 45-47 are pending. Claims 1-8, 14 and 45-47 are under consideration.

Specification

1. The disclosure is objected to because of the following informalities: The amendment filed 3-24-05 indicates that there are SEQ ID Nos. 39-41, however, there are only 2 nucleotide sequences in Figure 3A rather than 3 sequence of SEQ ID Nos. 39-41.

Appropriate correction is required.

Claim Rejections - 35 USC § 102

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

3. Claims 1-8 and 14 remain rejected under 35 U.S.C. 102(b) as being anticipated by Siegel et al., 2000 (Methods in Enzymology, Vol. 327, p. 249-259, IDS). Applicant's arguments filed 3-29-07 have been fully considered but they are not persuasive.

Applicant argues that reference Siegel does not teach or suggest random insertion and to produce a function GFP based sensor, insertion of the GFP sequence cannot occur in a random manner (amendment, p. 9-10). This is not found persuasive because of the reasons set forth in

Art Unit: 1632

the preceding Official action mailed 12-29-06. Siegel teaches that “[I]n general, we have found that the polymerase chain reaction (PCR) works well for inserting GFP into signal transduction proteins and that channel proteins, in particular, are surprisingly tolerant to GFP insertions. In the case of Shaker, we find that GFP can be inserted at the N terminal, at the C terminal, and also at a variety of internal sites. In our experience, these chimeric proteins are usually fluorescent, and the signal transduction protein usually functions.” (e.g. p. 256, 1st full paragraph). It appears that Siegel does suggest insert GFP into signal transduction protein and channel protein randomly at various different insertion sites and found that they are surprisingly tolerant to GFP insertions. Thus, the claims remain rejected under 35 U.S.C. 102(b).

4. Claims 1-8 and 14 remain rejected under 35 U.S.C. 102(b) as being anticipated by Lacatena et al., 1994 (PNAS, Vol. 91, pp. 10521-10525). Applicant's arguments filed 3-29-07 have been fully considered but they are not persuasive.

Applicant argues that the method taught by Lacatena is specific and does not teach or suggest that the transposition of TnphoA into the hubeta2AR gene occurs at a random position or in a random manner. Applicant further argues that specificity in the location of the hubeta2AR-PhoA fusion affected alkaline phosphatase activity (amendment, p. 11-12). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 12-29-06. Lacatena teaches using TnphoA, a transposon probe for protein export signals, to generate hubeta2AR-phoA fusion protein in vivo by transposition of TnphoA into the hubeta2AR gene in PUC18. Transposon insertion into a nucleotide sequence is a random event. The data in Figure 2 shows the result of numerous different random insertions by the transposon TnphoA. The

Art Unit: 1632

claims do not recite limitation that activity of the insertion sequence or acceptor sequence or its product should not be affected. Claim 1 recites “wherein insertion couples the state of the insertion sequence to the state of the acceptor sequence”. Claim 2 recites “wherein the state of the insertion sequence is modulated”. Claim 6 recites “wherein the fusion molecule comprises a new state”. The claims only require the state of the insertion sequence or acceptor sequence is modulated or the fusion molecule comprises a new state, which is what Lacatena taught.

Inserting an insertion sequence into an acceptor sequence creates new state for both insertion sequence and acceptor sequence, and the fusion molecule has a new state. Whether the activity of alkaline phosphatase is increased or decreased is irrelevant to the instant invention. Thus, claims 1-8 and 14 remain anticipated by Lacatena.

5. Claims 1-8 and 14 remain rejected under 35 U.S.C. 102(e) as being anticipated by Anderson et al., 2003 (US Patent No. 6,596,485 B2). Applicant's arguments filed 3-29-07 have been fully considered but they are not persuasive.

Applicant argues that '485 patent teaches particular positions in the acceptor sequence where insertion of the insertion sequence is preferred but fails to teach random insertion (amendment, p. 12-13). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 12-29-06. Anderson teaches “the library should provide a sufficiently structurally diverse population of randomized expression products to effect a probabilistically sufficient range of cellular response to provide one or more cells exhibiting a desired response” (e.g. column 5, lines 29-33) and “in a preferred embodiment, the peptide library is fully randomized with no sequence preference or constants at any position” (e.g.

Art Unit: 1632

column 6, lines 11-13). The condition cited by applicant is "preferred embodiment" and does not include other condition disclosed by Anderson. Anderson teaches that "any number of combinations of presentation structures, targeting sequences, rescue sequences, and stability sequences may be used, with or without linker sequences" (e.g. column 16, lines 52-56). Anderson teaches inserting peptide into GFP at numerous different positions, and the insertion is random. Thus, claims 1-8 and 14 remain anticipated by Anderson.

6. Claims 1-8 and 14 remain rejected under 35 U.S.C. 102(b) as being anticipated by Doi et al., 1999 (FEBS Letters, Vol. 453, p. 305-307). Applicant's arguments filed 3-29-07 have been fully considered but they are not persuasive.

Applicant argues that Doi teaches that several rounds of random mutagenesis must be performed in order to obtain polypeptide with increased fluorescence upon binding of ligand to BLIP, and Doi does not teach or suggest a method for assembling a modulatable fusion comprising random insertion of an insertion sequence into an acceptor sequence (amendment, p. 13-14). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 12-29-06. Random mutagenesis of the fusion GFP:Bla gene using error-prone PCR to obtain a plasmid library encompasses random insertion of an insertion sequence into an acceptor sequence. Thus, claims 1-8 and 14 remain anticipated by Doi.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Art Unit: 1632

Claims 45-47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicant's amendment filed 3-29-07 necessitates this new ground of rejection.

The phrase "one or more method selected from nuclease treatment...chemical treatment or radiation treatment" in claim 45 is vague and renders the claim indefinite. It is unclear whether the "radiation treatment" is included in the method selected or is excluded in the method selected. Changing the phrase to "one or more method **selected from the group consisting of** nuclease treatment...chemical treatment **and** radiation treatment" would be remedial.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 45-47 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant's amendment filed 3-29-07 necessitates this new ground of rejection.

The newly added claims 45-47 read on inserting randomly comprises one or more of a method selected from nuclease treatment, such as 3' to 5' exonuclease digestion, mechanical sheering, chemical treatment or radiation treatment. The phrase "one or more of a method selected from nuclease treatment, mechanical sheering, chemical treatment or radiation

Art Unit: 1632

treatment” is considered new subject matter. Applicant only points out that the amendment can be found throughout the specification and from the pending claims but fails to specifically disclose where the support for the phrase set forth above would be. Examiner is unable to find the support for the phrase set forth above in the specification or in the claims. Thus, the phrase set forth above is considered new matter. Similarly, the phrase “wherein nuclease treatment comprises digestion with a 3’ to 5’ exonuclease” is also considered new subject matter for the same reasons.

Claims 45-47 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The newly added claims 45-47 read on inserting randomly comprises one or more of a method selected from nuclease treatment, such as 3’ to 5’ exonuclease digestion, mechanical shearing, chemical treatment or radiation treatment. It was well known in the art that the methods of nuclease treatment, mechanical shearing, chemical treatment and radiation treatment are used to fragment a nucleotide sequence into smaller nucleotide sequences. It was well known in the art to insert a nucleotide sequence into another nucleotide sequence by using ligase so as to combine those two sequences. The specification fails to provide specific guidance and evidence for how to insert a sequence, such as nucleotide sequence, a protein sequence or a carbohydrate sequence, into another sequence by using nuclease treatment, such as 3’ to 5’ exonuclease digestion, mechanical shearing, chemical treatment or radiation treatment. There is

Art Unit: 1632

no evidence of record that shows nuclease treatment, such as 3' to 5' exonuclease digestion, mechanical sheering, chemical treatment or radiation treatment can insert an insertion sequence into an acceptor sequence to generate a fusion molecule. Absent such guidance, one skilled in the art at the time of the invention would not know how to practice the claimed invention and would require undue experimentation to practice over the full scope of the invention claimed.

For the reasons set forth above, one skilled in the art at the time of the invention would have to engage in undue experimentation to practice over the full scope of the invention claimed. This is particularly true based upon the nature of the claimed invention, the state of the art, the unpredictability found in the art, the teaching and working examples provided, the level of one of ordinary skill which is high, the amount of experimentation required, and the breadth of the claims.

Election/Restrictions

This application contains claims 26, 30, 32, 38, 39 and 41 drawn to an invention nonelected with traverse in the reply filed on 11-29-06. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Oath/Declaration

The new oath/declaration filed 4-25-07 has been entered and is acknowledged.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for this group is (571) 273-8300.

Art Unit: 1632

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Shin-Lin Chen, Ph.D.



SHIN-LIN CHEN
PRIMARY EXAMINER